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EXAMINER	
MUMMERT, STEPHANIE KANE	
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1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/16/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	10/748,713	REMACLE ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on January 18, 2007 is acknowledged and has been entered. Claims 1, 3, 7 and 12 have been amended. Claims 1-16 are pending.

Claims 1-16 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Previous Rejections

The objection to claim 7 is withdrawn in view of Applicant's amendment to the claims. The rejection of claim 3 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment to the claims. The rejection of claims 1-3, 6 and 15 under 35 USC 102(a) as being anticipated by Lee is withdrawn in view of Applicant's amendment to the claims. However, a new ground of rejection under 35 USC 103 in view of Langmann has been applied.

The rejection of claims 1-3, 5-6, 10 and 15-16 under 35 U.S.C. 102 as being anticipated by Watts is maintained in view of a broad interpretation of the term low-density microarray. However, in view of a more narrow interpretation of the term, a new 103 in view of Zammatteo will also be applied.

Claim Interpretation

The term 'low density microarray' is being given the broadest reasonable interpretation in view of the specification. The amendment to the claims states "said microarray contains capture probes to at least 5 ABC transporter subfamilies and wherein said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes". First, it is noted that the term 'containing' is being interpreted as comprising language. Therefore, the inclusion of the upper limit on the number of capture probes does not distinguish over art which teaches microarrays designed to assay and detect more than 3000 genes.

Next, the specification of the instant application discloses low-density microarrays but does not explicitly define what is meant by the term. Instead, the term is broadly described as "also known as a DNA chip or gene chip" (paragraph 91 of PgPub). Therefore, the term is being interpreted as reading on any microarray, including arrays characterized as 'high-density'.

Finally, it is noted that the claim will be interpreted in two ways regarding art-based rejections of the claims. For rejections where the reference teaches a microarray of any density for the analysis of ABC Transporter gene expression, but does not teach that the array is 'low-density', the broad interpretation of the amendment to the claim will be applied. Also new art rejections will also be applied using the more narrow interpretation of the term 'low-density array' provided in Applicant's remarks.

1. Claims 1-3, 5-6, 10 and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

With regard to claim 1, Watts teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

(i) providing a sample containing cells exposed or having been exposed to said active substance (p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines),

(ii) analyzing a gene expression pattern of said cells on a microarray (p. 435, col. 2, 'microarray preparation' heading, where cDNAs were printed onto chemically activated glass slides, including 5184 IMAGE consortium genes and 88 human housekeeping genes), said microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters, wherein said microarray contains capture probes to at least 5 ABC transporter subfamilies and wherein said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2, as published at http://biorag.org/perl/setseq.pl?id=5h; see attached sheets with representative entries for specific genes noted), wherein a change of the gene expression of said at least 5 ABC

transporters by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 436, col. 2, 'data analysis' heading, where fluorescence intensity measurements were taken and compared with background and elements with a signal below 1.4-fold background in one channel were designated as possible cases of a gene turned on or off and genes found to be differentially expressed in four of seven hybridizations comparing control RPM1 8226 with 8226/Dox40 was considered for relevance to drug resistant phenotype).

With regard to claim 2, Watts teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for at least 5, 10, 39 and 49 ABC transporters selected from those listed in Table 1 (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2).

With regard to claim 3, Watts teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern for at least 5 genes of the ABC transporter family having unravelled multi-drug resistance function as provided in Table 1 (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2).

With regard to claim 5, Watts teaches an embodiment of claim 1, wherein said drug is selected from Table 3 (Abstract, p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in

resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines, wherein the drug was doxorubicin).

With regard to claim 6, Watts teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (Abstract, p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines, wherein the drug was doxorubicin).

With regard to claim 10, Watts teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 434, col. 1, where it is noted that doxorubicin is important for the treatment of a variety of cancers)

With regard to claim 15, Watts teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides ((p. 435, col. 2, 'microarray preparation' heading, where cDNAs were printed onto chemically activated glass slides, including 5184 IMAGE consortium genes and 88 human housekeeping genes).

With regard to claim 16, Watts teaches an embodiment of claim 1, wherein each one specific location gives the quantification of one ABC transporters gene (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2, as published at http://biorag.org/perl/setseq.pl?id=5h).

Claim Rejections - 35 USC § 103

2. Claims 4, 10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of Nakayama et al. (Int J. Cancer, 2002, vol. 101, p. 488-495). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of the resistance of cells to a particular chemotherapy treatment in patient samples or the suitability of the treatment for the specific patient sample. Nakayama teaches an examination of the expression of multi-drug resistance genes in ovarian carcinoma (Abstract).

With regard to claim 4, Nakayama teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Figure 1, where the expression of multidrug resistance genes were examined in 82 patients with ovarian carcinoma; p. 489, 'patients and samples' heading, where these patients were primarily treated with surgery and postoperative chemotherapy, including cisplatin 60-70 mg/m^2, doxorubicin 40 mg/m^2 and cyclophosphamide 500 mg/body).

With regard to claim 10, Nakayama teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (Figure 1, where the expression of multidrug resistance genes were examined in 82 patients with ovarian carcinoma; p. 489, 'patients and samples' heading,

where these patients were primarily treated with surgery and postoperative chemotherapy, including cisplatin 60-70 mg/m^2, doxorubicin 40 mg/m^2 and cyclophosphamide 500 mg/body)

With regard to claim 14, Nakayama teaches an embodiment of claim 1, wherein said sample containing cells is from solid tumors (p. 489, col. 2, 'patient samples' heading, where surgical specimens from 82 patients with ovarian carcinoma were provided and where ovarian carcinoma is a solid tumor).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate specific patient samples, including ovarian carcinoma, as taught by Nakayama into the gene expression analysis disclosed by Watts with a reasonable expectation for success. Both Watts and Nakayama are centrally focused on the examination of the gene expression of genes associated with multi-drug resistance and have an interest in identifying gene targets that are specifically associated with resistance to specific chemotherapeutic drugs. Nakayama teaches "several genes including MDR1, MRP1, MRP2 and LRP genes have been identified to be responsible for resistance to various drugs" (p. 488, col. 1). Furthermore, Nakayama teaches that "during the past decade there have been a lot of studies linking various transporters to multidrug resistance both in cell culture and in clinic. Among such transporters MDR1, MRP1, MRP2, LRP and BCRP have gained considerable attention in cancer chemotherapy. We claim yet another transporter, ATP7B is involved in cisplatin drug resistance. We observed a high frequency of expressions of drug resistance-related transporters such as MDR1, MRP1, MRP2, LRP, BCRP and ATP7B gene in untreated human ovarian carcinoma." (p. 494, col. 1, 'discussion' heading). Therefore, considering the common experimental focus shared between Nakayama and Watts, it would have been prima facie

obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Nakyama to incorporate the microarray analysis taught by Watts or to have incorporated the patient samples and examination of drug resistance taught by Nakayama into the analysis disclosed by Watts with a reasonable expectation for success.

3. Claims 4 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of the resistance of cells to a particular chemotherapy treatment in patient samples or the suitability of the treatment for the specific patient sample. List teaches an examination of patient response to chemotherapeutic treatment and correlation to the expression of specific genes associated with multi-drug resistance (Abstract).

With regard to claim 4, List teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; see also Table 3).

With regard to claim 7, List teaches an embodiment of claim 6, wherein the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment (Table 4, where the change in drug resistance phenotype

after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 8, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising determining an activity of said drug against said cells (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 9, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising selecting of an active drug for patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 10, List teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 2465, col. 1, where the specific treatments of different types of chemotherapy regimens are described)

With regard to claim 12, List teaches an embodiment of claim 1, wherein said said sample containing cells is from acute myeloid leukemia (Figure 1, Table 1, where AML patient samples were studied).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the teachings of List, specifically directed to the association of multidrug resistance genes and patient response into the method of gene expression analysis of multi-drug resistance associated genes as taught by Watts with a reasonable expectation of success. As taught by List, "Clinical resistance to chemotherapy

results from the interaction of numerous biological variables. In this study, we found that overexpression of the novel major vault transporter protein, LRP, has prognostic significance in AML" (p. 2466, col. 2). Furthermore List teaches, "despite treatment and cohort heterogeneity, LRP was an important predictor of response to induction chemotherapy in patients with AML, independent of disease category. After adjusting for potential differences related to diagnostic group, LRP+ patients had a significantly lower remission rate and higher probability of resistant failure than did LRP- patients" (p. 2467, col. 1). While List examines the expression of the multidrug resistance genes using antibodies and immunohistochemistry and Watts teaches an analysis of expression at the level of mRNA using microarrays, it would have been obvious to one of ordinary skill in the art to apply the general experimental design taught by List, including an analysis of expression correlated with patient response, to include gene specific analysis in addition to analysis at the protein level. Therefore, one of ordinary skill in the art at the time that the invention was made would have been motivated to include the teachings by List, including the determination of resistance of specific patients to particular chemotherapeutic targets into the method of gene expression analysis taught by Watts with a reasonable expectation for success.

4. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of Dao et al. (Human Molecular Genetics, 1998, vol. 7, no. 4, p. 597-608). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of Kir6.1, Mr6.2 or IMPT1. Dao teaches the isolation and characterization of an imprinted gene located on chromosome 11p15.5, IMPT1 (Abstract).

With regard to claim 11, Dao teaches an embodiment of claim 1, wherein the assay contains at least one gene selected from Kir6.1, Mr6.2 and IMPT (p. 599, Figure 2, where the tissue specific expression of IMPT1 is examined).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the gene specific sequences analyzed by Watts to incorporate the specific gene, IMPT1, as taught by Dao. As taught by Dao, "IMPT1 (imprinted multi-membrane-spanning polyspecific transporter-like gene 1), located in this chromosomal domain between IPL and p57KIP2. This gene encodes a predicted protein with multiple membrane spanning segments which belongs to the polyspecific transporter/multi-drug resistance gene family" (p. 597, col. 2). Furthermore, Dao teaches that "The predicted IMPT1 protein identified many similar proteins in a Blastp analysis: all were members of a well-established family of membrane proteins with multiple membrane-spanning segments and with known or suspected polyspecific transport capabilities for small organic molecules" (p. 598, col. 2). Therefore, considering the stated goal of Watts of examing the expression of genes associated with multi-drug transport, one of ordinary skill in the art at the time the invention was made would have been motivated to include the additional target, IMPT1, into the gene expression analysis of resistance to chemotherapy drugs as taught by Watts with a reasonable expectation for success.

5. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of van den Heuvel-Eibrink et al. (International Journal of Pharmacology and Therapeutics). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of cells from acute myeloid leukemia or acute lymphocytic leukemia. Van den Heuvel-Eibrink teaches an overview of the role of membrane transport-associated multidrug resistance proteins in leukemia (Abstract).

With regard to claim 12, van den Heuvel-Eibrink teaches an embodiment of claim 1, wherein said said sample containing cells is from acute myeloid leukemia (p. 100-103, where the relevance of multidrug resistance and ALL and AML leukemias is discussed, specifically at p. 103, col. 2, it is noted that the coexpression of several drug resistance proteins seems to be highly predictive of clinical outcome. In AML, the expression of MRP and MDR-1 is correlated with complete remission and long-term survival).

With regard to claim 13, van den Heuvel-Eibrink teaches the method of claim 1, wherein said sample containing cells is from acute lymphocytic leukemia (p. 100-103, where the relevance of multidrug resistance and ALL and AML leukemias is discussed; specifically, at p. 100, col. 1, it is noted that the long-term survival for adults with ALL is 20%. Treatment failure is associated with clinical resistance to chemotherapy).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Watts to incorporate specific patient samples and particularly patient samples derived from patients affected by a variety of leukemias, including acute myeloid leukemia and/or acute lymphocytic leukemia. As taught by van den Heuvel-Eibrink, "In adults, AML is the most frequently occurring leukemia and the incidence of ALL is much lower. After a CR rate of 80%, the long-term survival for adults with ALL is only 20%. Treatment failure is associated with clinical resistance to chemotherapy and with cellular resistance in vitro determined by cell culture assays" (p. 100, col. 1). Furthermore, van den Heuvel-Eibrink teaches that "Expression of mdr-1 at transcriptional and a post-translational level, in de novo AML has been proven as an independent adverse prognostic factor with respect to CR and survival, especially in adults and this has led to clinical studies in adults with mdr-1 modifiers such as cyclosporin and PSC833" (p. 102, col. 2). Finally, van den Heuvel-Eibrink teaches that "Mdr-1 expression might play a more important role in adults. Only in childhood ALL has a high expression of LRP been found at time of relapse and this was in the cases of multiple relapse. Mdr-1 and LRP expression at diagnosis in AML patients is regarded as an independent prognostic factor for CR and long-term survival" (p. 103, col. 2, 'discussion' heading). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the additional tumor targets described by van den Heuvel-Eibrink or to apply the gene expression analysis by microarray taught by Watts to the specific tumor targets with a reasonable expectation for success.

6. Claims 1-3, 5-6, 10 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Chinese Journal of Cancer Research, 2002, 14(1), p. 5-10) in view of Annereau et al. (Proceedings of the American Association for Cancer Research, July 2003, vol. 44, 2nd ed, abstract #3992, p. 796-797). Wang teaches the use of cDNA microarrays to monitor gene expression profiles in drug resistant KB cells (Abstract).

With regard to claim 1, Wang teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

(i) providing a sample containing cells exposed or having been exposed to said active substance (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug),

(ii) analyzing a gene expression pattern of said cells on a microarray (p. 6, col. 1, 'fabrication of microarrays' and 'labeling, hybridization and scanning of microarrays' heading, where cDNA microarrays, consisting of a total of 12,720 PCR products, representing 2,640 randomly picked clones from a leukocyte cDNA library and 10,080 known genes), wherein a change of the gene expression by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 6, col. 2, 'results and discussion heading', where when labeled samples from KB-V1 cells and KB3-1 cells were co-hybridized to the array, on average approximately 0.68% of the cDNAs exhibit more than a 2-fold expression level change).

With regard to claim 5, Wang teaches an embodiment of claim 1, wherein said drug is selected from Table 3 (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug).

With regard to claim 6, Wang teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug).

With regard to claim 10, Wang teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug)

With regard to claim 15, Wang teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides (p. 6, col. 1, 'fabrication of microarrays' and 'labeling, hybridization and scanning of microarrays' heading, where cDNA microarrays, consisting of a total of 12,720 PCR products, representing 2,640 randomly picked clones from a leukocyte cDNA library and 10,080 known genes).

Regarding claim 1, Wang does not explicitly state that said microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters. Annereau

With regard to claim 1, Annereau teaches a microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters).

With regard to claim 2, Annereau in view of Wang teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for at least 5 or 10 ABC transporters selected from those listed in Table 1 (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters, where this collection of probes would overlap with at least 5-10 of the ABC transporters listed).

With regard to claim 3, Annereau in view of Wang teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern for at least 5 genes of the ABC transporter family having unravelled multi-drug resistance function as provided in Table 1 (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters, where this collection of probes would overlap with at least 5-10 of the ABC transporters listed).

With regard to claim 16, Annereau teaches an embodiment of claim 1, wherein each one specific location gives the quantification of one ABC transporters gene (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the array disclosed by Annereau into the analysis of gene expression changes in resistant cells treated with an anti-cancer drug as disclosed by Wang to arrive at the claimed invention with a reasonable expectation for success. As taught by Annereau, "our aim was to create a high-density microarray to explore different modes of

resistance against anticancer drugs. To a collection of genes known to play a role in detoxification, we added probes to detect the expression of the members of the ABC-transporter superfamily" (p. 796, abstract #3992, lines 1-4). Wang was also interested in the analysis of gene expression in multi-drug resistant cells using a cDNA microarray. As noted by Wang, "Several mechanisms of drug resistance in tumors have been proposed, including over-expression of the multidrug resistance gene (MDR1) and the multidrug resistance-associated proteins (MRP), and increased DNA damage repair" (p. 5). While Wang does not specifically note the inclusion or exclusion of these specific targets, MDR1 and/or MRP, both members of the ABC-transporter superfamily, the specific mention of their suspected role in drug resistance suggests that if these targets were not included, one of ordinary skill in the art would have been motivated to incorporate the 36 target sequences disclosed by Annereau with a reasonable expectation for success, in order to achieve an even more precise picture of the multiple genes involved in tumor progression and drug resistance.

New Grounds of Rejection necessitated by Applicant's amendments - with narrow interpretation of the amended claims

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, it is unclear what structural limitation is placed on the method by the addition of the term "low density microarray"? The amended claim recites "low density microarray containing capture probes for the detection of up to 3000 genes" however, the term containing is being read as comprising and therefore, more than 3000 probes could be present on the array and therefore the amendment does not impose a structural limitation on the array features.

Claim Rejections - 35 USC § 103

9. Claims 1-3, 6 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Journal of Pharmaceutical Sciences, 2003, vol. 92, no. 11, p. 2152-2163) in view of Langmann et al. (Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238). Lee teaches an examination of the expression of multi-drug resistance proteins by RT-PCR and microarray analysis (Abstract).

With regard to claim 1, Lee teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

(i) providing a sample containing cells exposed or having been exposed to said active substance (p. 2153-2154, 'MRP functional assay' heading, where cells were preincubated with or without 5-CDFA in the presence or absence of indomethacin; 'Rh123 efflux assay' heading, where cells

were preincubated with Rh123; 'tissue culture' heading, where cells were also incubated with IL-6, IL-1β, TNF-α),

(ii) analyzing a gene expression pattern of said cells on a microarray (p. 2154, col. 2, 'microarray studies' heading), said microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters wherein said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes (Figure 1, where MDR1/ABCB1 expression was analyzed in HuH7 cells, Figure 2, where MDR1/ABCB1 expression was analyzed in HepG2 cells, Figure 4C, where the expression of MRP1, MRP2, MRP3, MRP6 were measured in HepG2 cells; p. 2157, col. 2, where the microarray expression results were measured), wherein a change of the gene expression of said at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 2157, col. 2, where the microarray expression results were measured).

With regard to claim 2, Lee teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for at least 5, 10, 39 and 49 ABC transporters selected from those listed in Table 1 (Figure 1, where MDR1/ABCB1 expression was analyzed in HuH7 cells, Figure 2, where MDR1/ABCB1 expression was analyzed in HepG2 cells, Figure 4C, where the expression of MRP1, MRP2, MRP3, MRP6 were measured in HepG2 cells; p. 2157, col. 2, where the microarray expression results were measured).

With regard to claim 3, Lee teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern for at least 5 genes of the ABC transporter family having unravelled multi-drug resistance function as provided in Table 1 (Figure 1, where MDR1/ABCB1

expression was analyzed in HuH7 cells, Figure 2, where MDR1/ABCB1 expression was analyzed in HepG2 cells, Figure 4C, where the expression of MRP1, MRP2, MRP3, MRP6 were measured in HepG2 cells; p. 2157, col. 2, where the microarray expression results were measured).

With regard to claim 6, Lee teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (p. 2153-2154, 'MRP functional assay' heading, where cells were preincubated with or without 5-CDFA in the presence or absence of indomethacin; 'Rh123 efflux assay' heading, where cells were preincubated with Rh123; 'tissue culture' heading, where cells were also incubated with IL-6, IL-1β, TNF-α).

With regard to claim 15, Lee teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides (p. 2154-2155, 'microarray studies', where fluorescently labeled cDNA was hybridized onto Human 1.7K cDNA microarrays).

Regarding claim 1, while Lee teaches the examination of 5 ABC transporters, Lee does not teach that at least 5 ABC transporter subfamilies were detected. Langmann teaches the detection and profiling of the complete ABC-transporter superfamily in a variety of tissues through real-time reverse transcription expression analysis (Abstract).

With regard to claim 1, Langmann teaches an embodiment of claim 1, wherein said microarray contains capture probes to at least 5 ABC transporter subfamilies (Table 1, where gene specific primers and probes for all of the members of the ABC transporter superfamily are noted).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the method of expression analysis taught by Lee to

incorporate the variety of additional ABC transporter family targets as taught by Langmann to arrive at the claimed invention with a reasonable expectation for success. As taught by Langmann, "several ABC proteins in the human system are responsible for drug exclusion in compound-treated tumor cells providing cellular mechanisms for the development of multi-drug resistance". Langmann also states that there is a "need for a sensitive, rapid, and accurate method for quantification of ABC transporter expression and a systematic investigation of these molecules in human tissues is thus warranted" (p. 230-231). Langmann also notes "the aim of this study was to establish step by step, a complete panel of TaqMan RT-PCR assays for all 47 currently known human ABC molecules" (p. 231). Finally, Langmann notes "we provide comprehensive data on the expression of all human ABC transporter genes in various tissues" and while Langmann notes "TaqMan real-time RT-PCR is much more sensitive than blot-based mRNA analysis tools" because much less starting material is necessary prior to analysis, Langmann also notes "the results obtained from our assay are consistent with those obtained in Northern blot and in situ hybridization studies with single ABC molecules" (p. 237, col. 1, bottom of column). In comparison to Langmann, Lee teaches the analysis of MRP1, 2, 3 and 6 and MDR1 mRNA using RT-PCR and microarray analysis. Lee notes "the use of microarrays provides the speed, ease and feasibility of monitoring the differential expression profile of hundreds of genes." Lee also notes "it has been reported that cDNA microarray detection of large changes in gene expression is often comparable with data obtained from Northern blots" and states, too "a major strength of cDNA microarray technology is in its ability to rapidly detect large 10- to 100-fold increases in gene expression" (p. 2161, col. 1). Therefore, considering the combined teachings of Langmann and Lee, it would have been prima facie obvious to one of

ordinary skill in the art to extend the targets taught by Lee to incorporate additional ABC transporter sequences and tissue specific expression as taught by Langmann to achieve more comprehensive data regarding the role of additional ABC transporter family members in multi-drug resistance with a reasonable expectation for success.

10. Claims 1-3, 5-6, 10 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

With regard to claim 1, Watts teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

(i) providing a sample containing cells exposed or having been exposed to said active substance (p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines),

(ii) analyzing a gene expression pattern of said cells on a microarray (p. 435, col. 2, 'microarray preparation' heading, where cDNAs were printed onto chemically activated glass slides, including 5184 IMAGE consortium genes and 88 human housekeeping genes), said microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC

transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2, as published at http://biorag.org/perl/setseq.pl?id=5h; see attached sheets with representative entries for specific genes noted), wherein a change of the gene expression of said at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 436, col. 2, 'data analysis' heading, where fluorescence intensity measurements were taken and compared with background and elements with a signal below 1.4-fold background in one channel were designated as possible cases of a gene turned on or off and genes found to be differentially expressed in four of seven hybridizations comparing control RPM1 8226 with 8226/Dox40 was considered for relevance to drug resistant phenotype).

With regard to claim 2, Watts teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for at least 5, 10, 39 and 49 ABC transporters selected from those listed in Table 1 (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2).

With regard to claim 3, Watts teaches an embodiment of claim 1, wherein said at least 5 genes of the ABC transporter family are selected from the genes provided in Table 1 (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were

also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2).

With regard to claim 5, Watts teaches an embodiment of claim 1, wherein said drug is selected from Table 3 (Abstract, p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines, wherein the drug was doxorubicin).

With regard to claim 6, Watts teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (Abstract, p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines, wherein the drug was doxorubicin).

With regard to claim 10, Watts teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 434, col. 1, where it is noted that doxorubicin is important for the treatment of a variety of cancers)

With regard to claim 15, Watts teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides ((p. 435, col. 2, 'microarray preparation' heading, where cDNAs were printed onto chemically activated glass slides, including 5184 IMAGE consortium genes and 88 human housekeeping genes).

With regard to claim 16, Watts teaches an embodiment of claim 1, wherein each one specific location gives the quantification of one ABC transporters gene (Figure 2, where MDR1

and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2, as published at http://biorag.org/perl/setseq.pl?id=5h).

Regarding claim 1, Watts does not teach that said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes. Zammatteo teaches the use of a low-density microarray for the detection and monitoring of expression of MAGE-A genes.

With regard to claim 1, Zammatteo in view of Watts, teaches a low density microarray containing capture probes for the detection of up to 3000 genes (p. 28, col. 1-2, where the process of constructing the MAGE DNA microarrays is described).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the low density microarray format taught by Zammatteo into the method of detection of ABC transporters in multidrug resistance analysis to arrive at the claimed invention with a reasonable expectation for success. While Zammatteo discloses the use of these 'low density microarrays' for the detection of MAGE-A sequences specifically, for their role in tumor immunotherapy, the process of constructing and the process of analyzing the low-density microarray would be equally applicable and useful for the detection of ABC Transporter sequences or any other sequence of interest. As taught by Zammatteo, "the assay presented here can be considered an easy screening test to identify the MAGE-A genes expressed in a tumor sample" and this test is "very fast and avoids the use of hazardous compounds such as ethidium bromide". Furthermore, "because a single capture probe is used for each MAGE-A gene, the cost of the assay is reduced and the interpretation of the data is

straightforward, unlike high density microarrays, which rely on a pattern of hybridization to identify one target" (p. 31, col. 2). Therefore, considering the stated benefits of the specific low-density microarray format disclosed by Zammatteo one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the low density microarray format taught by Zammatteo to the detection of ABC transporter genes to achieve a straightforward and fast analysis of expression of these specific target sequences with a reasonable expectation for success.

11. Claims 4, 10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of Nakayama et al. (Int J. Cancer, 2002, vol. 101, p. 488-495). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammatteo teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 103 rejection stated above. Watts does not explicitly teach the examination of the resistance of cells to a particular chemotherapy treatment in patient samples or the suitability of the treatment for the specific patient sample. Nakayama teaches an examination of the expression of multi-drug resistance genes in ovarian carcinoma (Abstract).

With regard to claim 4, Nakayama teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Figure 1, where the expression of multidrug resistance genes were examined in 82 patients with ovarian carcinoma; p. 489, 'patients and samples' heading, where these patients were primarily

treated with surgery and postoperative chemotherapy, including cisplatin 60-70 mg/m^2, doxorubicin 40 mg/m^2 and cyclophosphamide 500 mg/body).

With regard to claim 10, Nakayama teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (Figure 1, where the expression of multidrug resistance genes were examined in 82 patients with ovarian carcinoma; p. 489, 'patients and samples' heading, where these patients were primarily treated with surgery and postoperative chemotherapy, including cisplatin 60-70 mg/m^2, doxorubicin 40 mg/m^2 and cyclophosphamide 500 mg/body)

With regard to claim 14, Nakayama teaches an embodiment of claim 1, wherein said sample containing cells is from solid tumors (p. 489, col. 2, 'patient samples' heading, where surgical specimens from 82 patients with ovarian carcinoma were provided and where ovarian carcinoma is a solid tumor).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate specific patient samples, including ovarian carcinoma, as taught by Nakayama into the gene expression analysis disclosed by Watts in view of Zammatteo with a reasonable expectation for success. Both Watts and Nakayama are centrally focused on the examination of the gene expression of genes associated with multi-drug resistance and have an interest in identifying gene targets that are specifically associated with resistance to specific chemotherapeutic drugs. Nakayama teaches "several genes including MDR1, MRP1, MRP2 and LRP genes have been identified to be responsible for resistance to various drugs" (p. 488, col. 1). Furthermore, Nakayama teaches that "during the past decade there have been a lot of studies linking various transporters to multidrug resistance both in cell culture and in clinic. Among

such transporters MDR1, MRP1, MRP2, LRP and BCRP have gained considerable attention in cancer chemotherapy. We claim yet another transporter, ATP7B is involved in cisplatin drug resistance. We observed a high frequency of expressions of drug resistance-related transporters such as MDR1, MRP1, MRP2, LRP, BCRP and ATP7B gene in untreated human ovarian carcinoma." (p. 494, col. 1, 'discussion' heading). Therefore, considering the common experimental focus shared between Nakayama and Watts, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Nakyama to incorporate the microarray analysis taught by Watts or to have incorporated the patient samples and examination of drug resistance taught by Nakayama into the analysis disclosed by Watts with a reasonable expectation for success.

12. Claims 4 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammatteo teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 103 rejection stated above. Watts does not explicitly teach the examination of the resistance of cells to a particular chemotherapy treatment in patient samples or the suitability of the treatment for the specific patient sample. List teaches an examination of patient response to

chemotherapeutic treatment and correlation to the expression of specific genes associated with multi-drug resistance (Abstract).

With regard to claim 4, List teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; see also Table 3).

With regard to claim 7, List teaches an embodiment of claim 6, wherein the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 8, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising determining an activity of said drug against said cells (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 9, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising selecting of an active drug for patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 10, List teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 2465, col. 1, where the specific treatments of different types of chemotherapy regimens are described)

With regard to claim 12, List teaches an embodiment of claim 1, wherein said said sample containing cells is from acute myeloid leukemia (Figure 1, Table 1, where AML patient samples were studied).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the teachings of List, specifically directed to the association of multidrug resistance genes and patient response into the method of gene expression analysis of multi-drug resistance associated genes as taught by Watts in view of Zammatteo with a reasonable expectation of success. As taught by List, "Clinical resistance to chemotherapy results from the interaction of numerous biological variables. In this study, we found that overexpression of the novel major vault transporter protein, LRP, has prognostic significance in AML" (p. 2466, col. 2). Furthermore List teaches, "despite treatment and cohort heterogeneity, LRP was an important predictor of response to induction chemotherapy in patients with AML, independent of disease category. After adjusting for potential differences related to diagnostic group, LRP+ patients had a significantly lower remission rate and higher probability of resistant failure than did LRP- patients" (p. 2467, col. 1). While List examines the expression of the multidrug resistance genes using antibodies and immunohistochemistry and Watts in view of Zammatteo teaches an analysis of expression at the level of mRNA using microarrays, it would have been obvious to one of ordinary skill in the art to apply the general experimental design taught by List, including an analysis of expression correlated with patient response, to include gene specific analysis in addition to analysis at the protein level. Therefore, one of ordinary skill in the art at the time that the invention was made would have been motivated to include the teachings by List, including the determination of resistance of specific patients to

particular chemotherapeutic targets into the method of gene expression analysis taught by Watts with a reasonable expectation for success.

13. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of Dao et al. (Human Molecular Genetics, 1998, vol. 7, no. 4, p. 597-608). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammatteo teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of Kir6.1, Mr6.2 or IMPT1. Dao teaches the isolation and characterization of an imprinted gene located on chromosome 11p15.5, IMPT1 (Abstract).

With regard to claim 11, Dao teaches an embodiment of claim 1, wherein the assay contains at least one gene selected from Kir6.1, Mr6.2 and IMPT (p. 599, Figure 2, where the tissue specific expression of IMPT1 is examined).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the gene specific sequences analyzed by Watts in view of Zammatteo to incorporate the specific gene, IMPT1, as taught by Dao. As taught by Dao, "IMPT1 (imprinted multi-membrane-spanning polyspecific transporter-like gene 1), located in this chromosomal domain between IPL and p57KIP2. This gene encodes a predicted protein with multiple membrane spanning segments which belongs to the polyspecific transporter/multi-drug resistance gene family" (p. 597, col. 2). Furthermore, Dao teaches that "The predicted

IMPT1 protein identified many similar proteins in a Blastp analysis: all were members of a well-established family of membrane proteins with multiple membrane-spanning segments and with known or suspected polyspecific transport capabilities for small organic molecules" (p. 598, col. 2). Therefore, considering the stated goal of Watts of examing the expression of genes associated with multi-drug transport, one of ordinary skill in the art at the time the invention was made would have been motivated to include the additional target, IMPT1, into the gene expression analysis of resistance to chemotherapy drugs as taught by Watts with a reasonable expectation for success.

14. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34) as applied to claims 1-3, 5-6, 10 and 15-16 above, and further in view of van den Heuvel-Eibrink et al. (International Journal of Pharmacology and Therapeutics). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammatteo teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of cells from acute myeloid leukemia or acute lymphocytic leukemia. Van den Heuvel-Eibrink teaches an overview of the role of membrane transport-associated multidrug resistance proteins in leukemia (Abstract).

With regard to claim 12, van den Heuvel-Eibrink teaches an embodiment of claim 1, wherein said said sample containing cells is from acute myeloid leukemia (p. 100-103, where the

relevance of multidrug resistance and ALL and AML leukemias is discussed, specifically at p. 103, col. 2, it is noted that the coexpression of several drug resistance proteins seems to be highly predictive of clinical outcome. In AML, the expression of MRP and MDR-1 is correlated with complete remission and long-term survival).

With regard to claim 13, van den Heuvel-Eibrink teaches the method of claim 1, wherein said sample containing cells is from acute lymphocytic leukemia (p. 100-103, where the relevance of multidrug resistance and ALL and AML leukemias is discussed; specifically, at p. 100, col. 1, it is noted that the long-term survival for adults with ALL is 20%. Treatment failure is associated with clinical resistance to chemotherapy).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Watts to incorporate specific patient samples and particularly patient samples derived from patients affected by a variety of leukemias, including acute myeloid leukemia and/or acute lymphocytic leukemia. As taught by van den Heuvel-Eibrink, "In adults, AML is the most frequently occurring leukemia and the incidence of ALL is much lower. After a CR rate of 80%, the long-term survival for adults with ALL is only 20%. Treatment failure is associated with clinical resistance to chemotherapy and with cellular resistance in vitro determined by cell culture assays" (p. 100, col. 1). Furthermore, van den Heuvel-Eibrink teaches that "Expression of mdr-1 at transcriptional and a post-translational level, in de novo AML has been proven as an independent adverse prognostic factor with respect to CR and survival, especially in adults and this has led to clinical studies in adults with mdr-1 modifiers such as cyclosporin and PSC833" (p. 102, col. 2). Finally, van den Heuvel-Eibrink teaches that "Mdr-1 expression might play a more important role in adults. Only

in childhood ALL has a high expression of LRP been found at time of relapse and this was in the cases of multiple relapse. Mdr-1 and LRP expression at diagnosis in AML patients is regarded as an independent prognostic factor for CR and long-term survival" (p. 103, col. 2, 'discussion' heading). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the additional tumor targets described by van den Heuvel-Eibrink or to apply the gene expression analysis by microarray taught by Watts to the specific tumor targets with a reasonable expectation for success.

15. Claims 1-3, 5-6, 10 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Chinese Journal of Cancer Research, 2002, 14(1), p. 5-10) in view of Annereau et al. (Proceedings of the American Association for Cancer Research, July 2003, vol. 44, 2nd ed, abstract #3992, p. 796-797) and further in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34). Wang teaches the use of cDNA microarrays to monitor gene expression profiles in drug resistant KB cells (Abstract).

With regard to claim 1, Wang teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

(i) providing a sample containing cells exposed or having been exposed to said active substance (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug),

(ii) analyzing a gene expression pattern of said cells on a microarray (p. 6, col. 1, 'fabrication of microarrays' and 'labeling, hybridization and scanning of microarrays' heading, where cDNA

microarrays, consisting of a total of 12,720 PCR products, representing 2,640 randomly picked clones from a leukocyte cDNA library and 10,080 known genes), wherein a change of the gene expression by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 6, col. 2, 'results and discussion heading', where when labeled samples from KB-V1 cells and KB3-1 cells were co-hybridized to the array, on average approximately 0.68% of the cDNAs exhibit more than a 2-fold expression level change).

With regard to claim 5, Wang teaches an embodiment of claim 1, wherein said drug is selected from Table 3 (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug).

With regard to claim 6, Wang teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug).

With regard to claim 10, Wang teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-VI was treated with 200 ng/ml vinblastin, an anti-cancer drug)

With regard to claim 15, Wang teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides (p. 6, col. 1, 'fabrication of microarrays' and 'labeling,

hybridization and scanning of microarrays' heading, where cDNA microarrays, consisting of a total of 12,720 PCR products, representing 2,640 randomly picked clones from a leukocyte cDNA library and 10,080 known genes).

Regarding claim 1, Wang does not explicitly state that said microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters.

With regard to claim 1, Annereau teaches a microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters).

With regard to claim 2, Annereau in view of Wang teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for at least 5 or 10 ABC transporters selected from those listed in Table 1 (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters, where this collection of probes would overlap with at least 5-10 of the ABC transporters listed).

With regard to claim 3, Annereau in view of Wang teaches an embodiment of claim 1, wherein said at least 5 genes of the ABC transporter family are selected from the genes provided in Table 1 (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters, where this collection of probes would overlap with at least 5-10 of the ABC transporters listed).

With regard to claim 16, Annereau teaches an embodiment of claim 1, wherein each one specific location gives the quantification of one ABC transporters gene (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters).

Regarding claim 1, neither Wang or Annereau teach that said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes. Zammatteo teaches the use of a low-density microarray for the detection and monitoring of expression of MAGE-A genes.

With regard to claim 1, Zammatteo in view of Wang and Annereau, teaches a low density microarray containing capture probes for the detection of up to 3000 genes (p. 28, col. 1-2, where the process of constructing the MAGE DNA microarrays is described).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the array disclosed by Annereau into the analysis of gene expression changes in resistant cells treated with an anti-cancer drug as disclosed by Wang to arrive at the claimed invention with a reasonable expectation for success. As taught by Annereau, "our aim was to create a high-density microarray to explore different modes of resistance against anticancer drugs. To a collection of genes known to play a role in detoxification, we added probes to detect the expression of the members of the ABC-transporter superfamily" (p. 796, abstract #3992, lines 1-4). Wang was also interested in the analysis of gene expression in multi-drug resistant cells using a cDNA microarray. As noted by Wang, "Several mechanisms of drug resistance in tumors have been proposed, including over-expression of the multidrug resistance gene (MDR1) and the multidrug resistance-associated proteins (MRP), and increased DNA damage repair" (p. 5). While Wang does not specifically

note the inclusion or exclusion of these specific targets, MDR1 and/or MRP, both members of the ABC-transporter superfamily, the specific mention of their suspected role in drug resistance suggests that if these targets were not included, one of ordinary skill in the art would have been motivated to incorporate the 36 target sequences disclosed by Annereau with a reasonable expectation for success, in order to achieve an even more precise picture of the multiple genes involved in tumor progression and drug resistance.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the low density microarray format taught by Zammatteo into the method of detection of ABC transporters in multidrug resistance analysis taught by Wang in view of Annereau to arrive at the claimed invention with a reasonable expectation for success. While Zammatteo discloses the use of these 'low density microarrays' for the detection of MAGE-A sequences specifically, for their role in tumor immunotherapy, the process of constructing and the process of analyzing the low-density microarray would be equally applicable and useful for the detection of ABC Transporter sequences or any other sequence of interest. As taught by Zammatteo, "the assay presented here can be considered an easy screening test to identify the MAGE-A genes expressed in a tumor sample" and this test is "very fast and avoids the use of hazardous compounds such as ethidium bromide". Furthermore, "because a single capture probe is used for each MAGE-A gene, the cost of the assay is reduced and the interpretation of the data is straightforward, unlike high density microarrays, which rely on a pattern of hybridization to identify one target" (p. 31, col. 2). Therefore, considering the stated benefits of the specific low-density microarray format disclosed by Zammatteo one of ordinary skill in the art at the time the invention was made would have been motivated to

incorporate the low density microarray format taught by Zammatteo to the detection of ABC transporter genes to achieve a straightforward and fast analysis of expression of these specific target sequences with a reasonable expectation for success.

Response to Arguments

Applicant's arguments filed January 18, 2007 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims 1-3, 6 and 15 Under 35 U.S.C. 102(a) as being anticipated by Lee et al. Applicant's arguments with respect to claims 1-3, 6 and 15 have been considered but are moot in view of the new ground(s) of rejection under 35 U.S.C. 103(a) as being unpatentable over Lee in view of Langmann as recited above.

Applicant traverses the rejection of claims 1-3, 5-6, 15 and 15 under 35 U.S.C. 102(b) as being anticipated by Watts et al. Applicant asserts that "Figure 1 and Table 1 of Watts et al. lists several genes having, with the exception of MDR1 and ABC Transporter 1, functions different from ABC Transporters. Furthermore, Watts et al. uses a high-density microarray, as evidenced on page 436, right column under 'microarray fabrication', having probes to more than 5,000 genes on the array" (p. 5 of remarks).

Regarding the contention by Applicant that Watts does not teach the analysis of 5 ATP binding cassette (ABC) transporter subfamilies, Applicant is directed to the portion of the previous action which provides more detail regarding the specific probes present on the microarray taught by Watts. Specifically, "multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1,

B10, ABC C2, C13, ABC D3, ABC E1, ABC E2" as published online based on the teachings under the 'microarray fabrication' heading of the materials and methods section of Watts, where a list of the specific clones on the microarray are listed (see list provided with previously mailed action). Regarding the inclusion of a high-density microarray in the teachings of Watts, this argument is not persuasive because, as noted in the claim interpretation stated above, the specification of the instant application discloses low-density microarrays but does not explicitly define what is meant by the term. Instead, the term is broadly described as "also known as a DNA chip or gene chip" (paragraph 91 of PgPub). Therefore, the term is being interpreted as reading on any microarray, including arrays characterized as 'high-density'. Furthermore, the amendment to the claim states "said microarray contains capture probes to at least 5 ABC transporter subfamilies and wherein said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes." The term 'containing' is being interpreted as comprising language and therefore, the inclusion of a proposed upper limit on the number of genes detected does not distinguish low-density arrays over arrays taught specifically as 'high-density' arrays.

Applicant traverses the rejection of claims 4 and 7-14 under 35 U.S.C. 103(a) as being unpatentable over a combination of Watts in view of Nakayama (Claim 4, 10, 14); a combination of Watts in view of List (4 and 7-9); a combination of Watts and Dao (11); and a combination of Watts and van den Heuvel-Eibrink (12-13).

Applicant asserts "Watts does not teach quantification of at least 5 ABC transporters on a low density microarray. The cited secondary references of Nakayama, List, Dao and van den Heuvel fail to cure the deficiencies of the main reference". Applicant goes on to list the specific

teachings of Nakayama, List, Dao and van den Heuvel respectively. These arguments are not persuasive because as noted in the arguments above, Watts does teach the analysis of at least 5 ABC transporters using an array and the arguments regarding the term 'low density microarray' have also been addressed previously.

Finally, Applicant traverses the rejection of claims 1-3, 5-6, 15 and 16 under 35 U.S.C. 103(a) as being unpatentable over a combination of Wang in view of Annereau. Applicant asserts "the combination of these references does not teach or suggest using a low-density microarray (no more than 3,000 probes) having capture probes specific for at least 5 ABC transporter subfamilies, is silent about a change in gene expression of at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference". These arguments are not persuasive. Regarding the arguments asserting a lack of a teaching or suggestion of using a low-density microarray have been addressed above regarding the Watts reference, but will be reiterated here. As noted in the claim interpretation stated above, the specification of the instant application discloses low-density microarrays but does not explicitly define what is meant by the term. Instead, the term is broadly described as "also known as a DNA chip or gene chip" (paragraph 91 of PgPub). Therefore, the term is being interpreted as reading on any microarray, including arrays characterized as 'high-density'. Furthermore, the amendment to the claim states "said microarray contains capture probes to at least 5 ABC transporter subfamilies and wherein said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes." The term 'containing' is being interpreted as comprising language and therefore, the inclusion of a proposed upper limit on the number of genes detected does not distinguish low-density arrays over arrays taught specifically as 'high-density' arrays.

Regarding the assertion that Annereau is silent regarding a change in gene expression of at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference, it is noted that Applicant's assertion regarding Annereau is not relevant to the rejection as that element of the claim was not addressed through the teachings of Annereau, but through the teachings of Wang. Wang explicitly teaches the detection of a more than 2-fold expression difference for specific cDNA sequences. However, addressing these arguments regarding Annereau, it is noted that a factor of at least about 1.5 represents a very small change in expression as detected by a microarray. Any variation in expression detected by either Wang or Annereau implies that the change represents at least about a 1.5 fold change in expression as compared to a reference sample.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert, Ph.D. whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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